MMHCC
the Mouse Models
of Human Cancers Consortium

MMHCC Newsletter June 2006

MouseLine

RNA Interference Stops Colon Cancer Spread In Mice

Using one of the newest and most powerful tools of biomedical science, University of Texas Medical Branch at Galveston (UTMB) researchers have scored a dramatic success in the battle against colorectal cancer.

The scientists were the first to use what are known as "small interfering RNAs" to block the spread of human colorectal cancer cells implanted in laboratory mice. Small interfering RNAs (siRNAs), first described in 2001, are tiny bits of genetic material that can prevent the translation of genes into proteins -- including specific proteins involved in biochemical reactions that promote cancer and other diseases.

According to the federal Centers for Disease Control and Prevention, colorectal cancer is the country's second leading cancer killer. In 2002, the most recent year for which statistics are available, 70,651 men and 68,883 women were diagnosed with the colorectal cancer in the United States; 28,471 men and 28,132 women died from the disease.

"What's exciting about this is that by using siRNAs we were able to selectively block components of the PI3K pathway, a biochemical pathway that is activated in a number of cancers, and suppress the spread of colon cancer in experimental animals," said UTMB professor of surgery B. Mark Evers, senior author of a paper on the research published in the June issue of Annals of Surgery. "Over the last couple of years people have talked a lot about cell-culture studies of siRNAs, but only a handful of labs have pushed it to animal models, which we need to do before going on to clinical trials."

To study the effects of siRNAs targeted against the PI3K pathway in mice, the researchers used a well-established technique in which human colorectal cancer cells were implanted into the spleens of genetically engineered immune-deficient "nude" mice. They then injected siRNAs designed to prevent the production of two specific PI3K proteins into the mice. The result was a major reduction in the spread of colorectal cancer to the liver.

Evers and the paper's other authors -- UTMB research fellows Piotr Rychahou and Lindsey Jackson and pathology professor Srinivasan Rajaraman -- also conducted a detailed analysis of the PI3K pathway's components and did experiments to determine how their siRNAs would affect colorectal cancer cell cultures. Scientists have already developed chemical inhibitors to attack the pathway (some of which are now in clinical trials), but toxic side effects limit their use.

"When we treat with siRNA and then follow the treatment with standard chemotherapeutic agents, we can markedly increase the rate at which cancer cells are killed," Evers said. "Since we have not seen any toxicity with these siRNAs in our mice, we think we can potentially also use them as a way to sensitize tumors and launch a combined attack that will allow us to achieve much better results with reduced side effects."

Source: Science Daily 05/24/2006, http://www.sciencedaily.com/releases/2006/05/060524124401.htm

Publication: Rychahou PG, Murillo CA, Evers BM. Targeted RNA interference of PI3K pathway components sensitizes colon cancer cells to TNF-related apoptosis-inducing ligand (TRAIL).
Surgery. 2005 Aug; 138(2):391-7.

RNA Interference Technique Causes Toxicity in Mice

The idea of silencing aberrant gene expression by interfering with the RNA product after transcription holds promise in the field of cancer gene therapy. One possible technique under study for RNA interference is the delivery of short hairpin RNA strands (shRNA) that are complementary to the target aberrant RNA, by way of a viral vector. However, a study published in the May 25 *Nature* highlights the risk of unintentional inhibition of cellular microRNA (miRNA) by shRNA overexpression, which led to fatalities in mice.

The investigators transfected mice with high doses of shRNA and found that the resulting toxicity was also high - 36 out of 49 shRNAs tested caused severe toxicity, and almost half of all shRNAs tested caused mortality within 2 months due to liver damage. This toxicity was not restricted to a particular shRNA sequence or target.

After further experiments to clarify the cause of the toxicity, the investigators found evidence of oversaturation of the endogenous shRNA processing machinery. This processing machinery is also needed by normal cellular miRNAs, which play an important role in the cell cycle and cellular development. The authors "therefore speculated that highly expressed 'toxic' shRNAs competed with miRNAs for intracellular processing, to such an extent that affected cells died."

Additional *in vivo* and *in vitro* experiments provided more evidence for this competition model, and identified a protein - nuclear karyopherin exportin-5 - that is likely a limiting factor in the shared processing pathway. The investigators caution that, in future use of shRNA, "monitoring and controlling intracellular shRNA levels is imperative for guaranteeing stable *in vivo* gene silencing while mitigating adverse effects."

Source: NCI Bulletin, May 30, 2006

Publication: Dirk Grimm, Konrad L. Streetz , Catherine L. Jopling, Theresa A. Storm, Kusum Pandey, Corrine R. Davis, Patricia Marion, Felix Salazar and Mark A. Kay
Fatality in mice due to oversaturation of cellular microRNA/short hairpin RNA pathways
Nature 441, 537-541 (25 May 2006)

Meetings

June 28, 2006, 8:00-12:00 PM Pacific Time
Mouse Models Of Human Cancers: New Models, New Opportunities
Seattle, WA
Meeting organizer: Norman Greenberg (ngreenberg@fhcrc.org)

View live webcast at: http://www.fhcrc.org/MMHCC
The meeting agenda can be found on the last page of this newsletter.

August 30 - September 2, 2006
Fifth Annual Meeting of the Society for Molecular Imaging
Big Island of Hawaii
Meeting information: http://www.molecularimaging.org

Meetings cont.

September 10 - 17, 2006
5th Annual Workshop on the Pathology of Mouse Models for Human Disease
Seattle, Washington
Workshop organizer: Robert Hackman, MD (rhackman@seattlecca.org)

September 15 - 18, 2006
25th Congress of the International Association for Breast Cancer Research
Montreal, Quebec, Canada
Meeting information: http://www.iabcr.com

Funding Opportunities

Collaborative Studies on Lung Stem Cell Biology and Cell Based Therapy (R01)
(RFA-HL-07-003)
National Heart, Lung, and Blood Institute
http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-07-003.html

In vivo Cancer Imaging Exploratory/Developmental Grants (R21)
(PA-06-371)
National Cancer Institute
http://grants.nih.gov/grants/guide/pa-files/PA-06-371.html

Innovative Technologies for Molecular Analysis of Cancer (R21)
(RFA-CA-07-015 and RFA-CA-07-016)
National Cancer Institute
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-015.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-016.html

Application of Emerging Technologies for Cancer Research
(RFA-CA-07-017, RFA-CA-07-018, and RFA-CA-07-019)
National Cancer Institute
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-017.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-018.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-019.html

New Technologies for Liver Disease STTR
(PA-06-396 and PA-06-397)
Multiple institutes
http://grants.nih.gov/grants/guide/pa-files/PA-06-396.html
http://grants.nih.gov/grants/guide/pa-files/PA-06-397.html

Funding Opportunities cont.

Innovations in Cancer Sample Preparation
(RFA-CA-07-022, RFA-CA-07-023, and RFA-CA-07-024)
National Cancer Institute
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-022.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-023.html
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-024.html

Novel Technologies For In Vivo Imaging
(PA-06-398 and PA-06-399)
National Cancer Institute
http://grants.nih.gov/grants/guide/pa-files/PA-06-398.html
http://grants.nih.gov/grants/guide/pa-files/PA-06-399.html

In Vivo Cellular and Molecular Imaging Centers (ICMICs)[P50]
(PAR-06-406)
National Cancer Institute
http://grants.nih.gov/grants/guide/pa-files/PAR-06-406.html

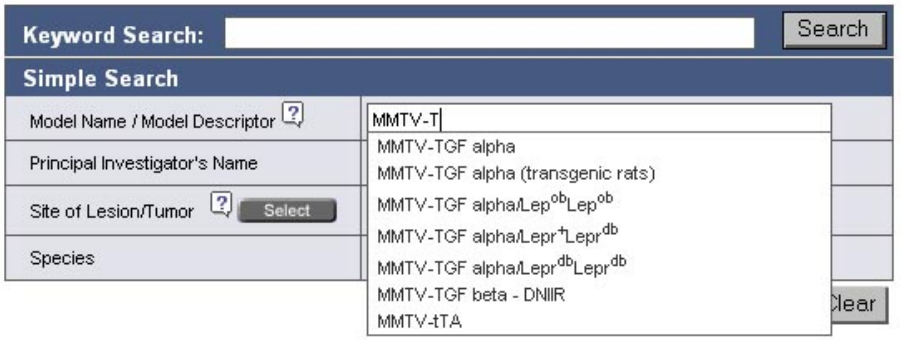
Bioinformatics

caMOD 2.1. release
The National Cancer Institute's Center for Bioinformatics announces the release of version 2.1 of caMOD, the cancer models database (http://cancermodels.nci.nih.gov/).
New features include:

- Added Transient Interference section to support Zebrafish models.
- The keyword searched for is now highlighted in yellow on the search results pages.

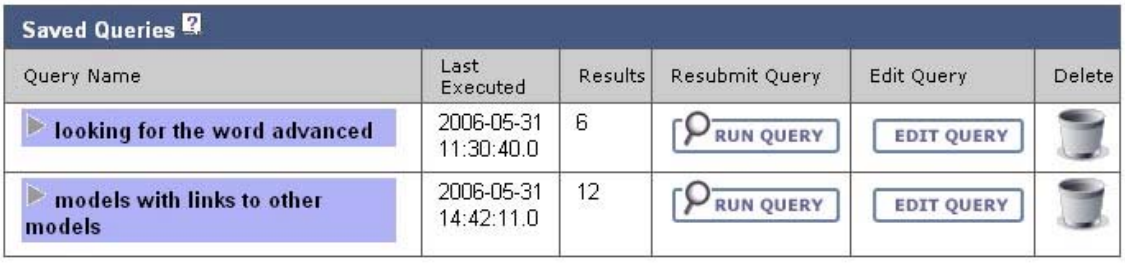
Phenotype	Intact cyclin D1 functions are essential for transformation by erbB2 in tissue culture and murine models. Because cyclin D1 may alter cell proliferation through a variety of mechanisms, we used transgenic models and human tumor samples to particularly address the role of cyclin D1-cyclin-dependent kinases in transformation by erbB2. The p16 tumor suppressor specifically blocks cyclin-dependent kinase 4 and 6 activity. Here we show that an MMTV-p16 transgene blocked tumorigenesis by erbB2, demonstrating that deregulation of the cyclin-dependent kinase partner of cyclin D1 is an essential target of erbB2. ErbB2 overexpression was a determining factor in deregulation of cyclin D1-cdk4/6 interactions because neither transgenic cyclin D1 nor loss of p16 accelerated tumorigenesis in MMTV-erbB2-transgenic mice. ErbB2 was also a deciding factor in deregulation of cyclin D1-cdk4/6 in human tumors because no loss of pRb or p16 was found in tumors overexpressing erbB2, although erbB2-negative invasive breast adenocarcinomas frequently lacked expression of p16 or pRb. We conclude that deregulation of cyclin D1-Cdk4/6 interactions is a critical target of erbB2 function in human and mouse breast tumors, and erbB2's overexpression may be sufficient to deregulate cyclin D1-cdk4/6 activity in breast cancer. Related models MMTV-erbB2 x MMTV-cyclin D1; MMTV-erbB2 x INK4A/ARF-/-

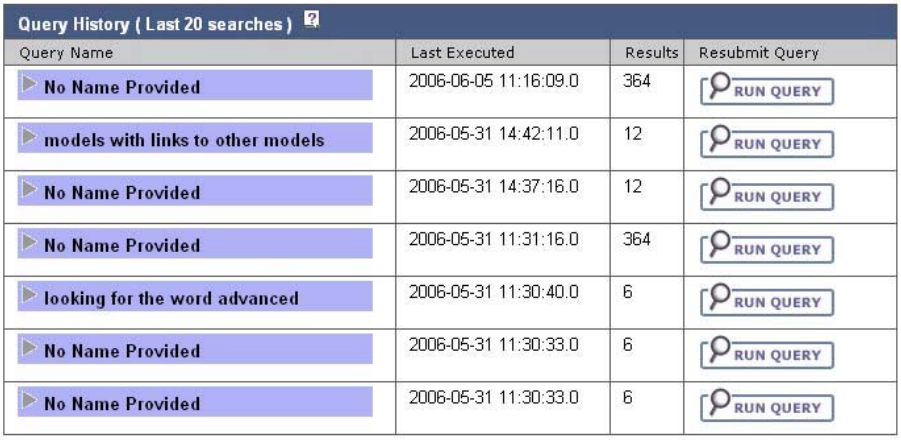
- The simple search now prompts the user with appropriate model descriptor/organ information based on the available models.



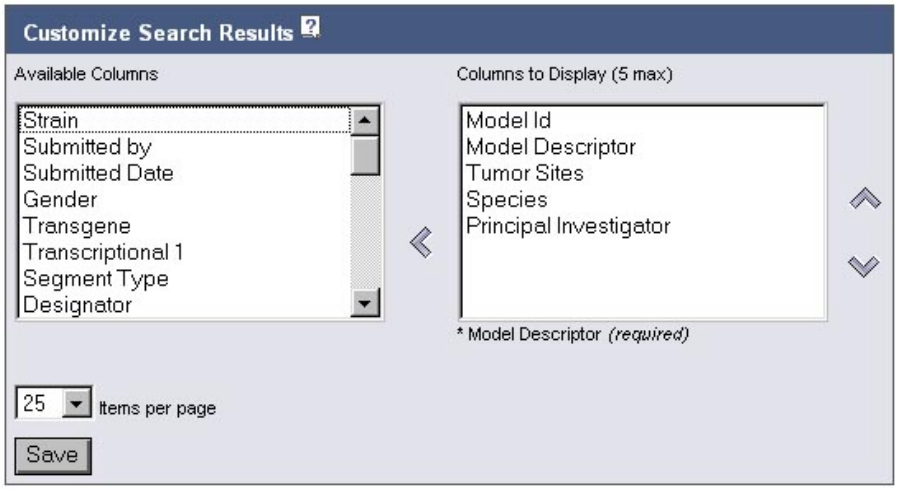
- The advanced search now prompts the user with appropriate model descriptor/organ/disease information based on the available models.
- The drug screening search now prompts the user with appropriate NSC numbers based on the available data.

A logged in user can view his/her query history as well as save particularly interesting queries for later use.





- The search results list is now configurable. A logged in user can customize the search results by selecting the number of results per page, and the information displayed on the search results screen.



- The caMOD 2.1 Common Data Elements (CDEs) are available via caDSR (cancer Data Standard Repository) http://ncicb.nci.nih.gov/core/caDSR

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A LIFE OF SCIENCE

Mouse Models Of Human Cancers: New Models, New Opportunities

NATIONAL CANCER INSTITUTE
MMHCC Mouse Models of Human Cancers Consortium

The Fred Hutchinson Cancer Research Center
Pelton Auditorium
June 28, 2006
08:00 AM - 12:00 PM Pacific Time

With Simultaneous Live Webcast http://www.fhcrc.org/MMHCC

AGENDA

0800 - 0815	Arrivals		
0815 - 0830	Dr. Norm Greenberg, Member, FHCRC Dr. Jim Roberts, Director, Basic Sciences Division		Welcome Introduction
0830 - 0900		Dr. William Grady Assistant Member, FHCRC	Modeling the initiation and progression of colon cancer from adenomas to metastatic disease
0900 - 0930		Dr. Jim Olson Associate Member, FHCRC	Targeted Therapies And Imaging In The SmoA Meduloblastoma Model
0930 - 1000		Dr. Amanda Paulovich Assistant Member, FHCRC	Assessing Biomarker Discovery Technologies Using Mouse Models Of Human Cancer
1000 - 1030		Dr. Sunil Hingorani Assistant Member, FHCRC	Mouse Models Of Preinvasive, Invasive And Metastatic Pancreatic Cancer
1030 - 1045	Coffee Break		
1045 - 1115		Dr. Chris Kemp Member, FHCRC	Autochthonous Tumor Models to Study The Role of p53 In Therapy Response
1115 - 1145		Dr. Jim Roberts Member, FHCRC Director, Basic Sciences Division	Cyclin Dependent Kinases And Cancer
1145 - 1200	Closing Remarks and Adjournment		

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